Brief report: cobicistat compared with ritonavir as a pharmacoenhancer for atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate: week 144 results

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Abstract: BACKGROUND: Cobicistat (COBI) is a pharmacoenhancer with no antiretroviral activity. METHODS: International, randomized double-blind active-controlled trial to evaluate the efficacy and safety of COBI vs ritonavir (RTV) as a pharmacoenhancer of atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate in HIV treatment-naive patients followed through week 144. RESULTS: At Week 144, virologic suppression was achieved in 72% (COBI) and 74% (RTV) of patients. Adverse events leading to study drug discontinuation occurred in 11% of patients in each group. Median changes in serum creatinine (mg/dL) were +0.13 (COBI) and +0.07 (RTV) and were unchanged from week 48. CONCLUSIONS: Once-daily COBI is a safe and effective pharmacoenhancer of the protease inhibitor atazanavir.

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Cobicistat Compared With Ritonavir as a Pharmacoenhancer for Atazanavir in Combination With Emtricitabine/Tenofovir Disoproxil Fumarate: Week 144 Results

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Background: Cobicistat (COBI) is a pharmacoenhancer with no antiretroviral activity.

Methods: International, randomized double-blind active-controlled trial to evaluate the efficacy and safety of COBI vs ritonavir (RTV) as a pharmacoenhancer of atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate in HIV treatment-naive patients followed through week 144.

Results: At Week 144, virologic suppression was achieved in 72% (COBI) and 74% (RTV) of patients. Adverse events leading to study drug discontinuation occurred in 11% of patients in each group. Median changes in serum creatinine (mg/dL) were +0.13 (COBI) and +0.07 (RTV) and were unchanged from week 48.

Conclusions: Once-daily COBI is a safe and effective pharmacoenhancer of the protease inhibitor atazanavir.

Key Words: Cobicistat, pharmacoenhancer, HIV, Antiretroviral, clinical trial

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INTRODUCTION

Cobicistat (COBI) is a pharmacoenhancer of protease inhibitors (PIs) or elvitegravir (EVG). COBI has a lower potential for off-target drug interactions than the standard boosting agent ritonavir (RTV), because of its more selective inhibition of cytochrome CYP3A and lower likelihood for enzymatic induction.[1,2] Unlike RTV, it has no anti-HIV activity. The 144-week safety and efficacy of the single-tablet regimen of EVG/COBI/emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) has been previously demonstrated.[3]

The safety and efficacy of COBI vs RTV as a pharmacoenhancer for atazanavir (ATV) in combination with FTC and TDF was evaluated in a randomized phase 3 trial (study GS-216-114). Week 48 clinical data demonstrated that COBI was safe, well-tolerated, and noninferior to RTV.[3] Here, we present the week 144 safety and efficacy data from study GS-US-216-0114 (clinical trials registration NCT01108510).

METHODS

A full description of the methods has been published.[4] Briefly, this international phase 3 double-blind and double-dummy study was approved by institutional review board at all investigative centers. Participants were HIV-1–infected adults with plasma HIV-1 RNA ≥5000 copies per milliliter and no previous use of antiretroviral agents. Key inclusion criteria included an estimated glomerular filtration rate (eGFR) of at least 70 mL/min and genotypic sensitivity to ATV, FTC, and TDF at screening. Eligible patients were randomized 1:1 to receive either COBI or RTV and matching

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placebo, each administered once daily with ATV plus FTC/TDF. After week 48, study visits occurred every 12 weeks until week 144. In patients taking study drugs with confirmed virologic rebound of HIV-1 RNA ≥400 copies per milliliter, genotype and phenotype assays were performed on the confirmatory sample (Monogram Biosciences, South San Francisco, CA). Efficacy was determined as the proportion of patients with virologic suppression (HIV-1 RNA <50 copies/mL) at week 144 using the US Food and Drug administration–defined snapshot analysis.

RESULTS

A total of 692 patients were randomized and treated: 344 in the COBI group and 348 in the RTV group. Demographic and general baseline characteristics, and safety and efficacy through week 48 have been reported previously.[4]

Virologic responses in the COBI group were comparable with the RTV group (COBI, 72.1%; RTV, 74.1%) at week 144 (Fig. 1). Mean increases in CD4 cell count at week 144 were similar in the 2 groups (+310 and +332 cells per μL). Development of resistance to the study regimens was infrequent through week 144; 3 patients in the COBI group and 1 in the RTV group developed resistance to FTC. No patients developed resistance to either PI or TDF.

The overall safety findings through week 144 were consistent with those through week 48. Similar percentages of patients in each group reported an adverse event (AE) (COBI, 96.5% and RTV, 95.7%). The most commonly reported AEs in the COBI group were diarrhea (22.4%), jaundice (21.8%), and scleral icterus (19.8%), and in RTV group were diarrhea (27.6%), scleral icterus (21.8%), and nasopharyngitis (20.7%) (Table 1). The most common AEs related to the study drug were due to elevated bilirubin, which occurred in a similar percentage of patients in the COBI and RTV groups (43.6% vs 41.4%); these were also the most common AEs leading to discontinuation in both groups (4.9% vs 4.0%). Rates of diarrhea and nausea were similar between the 2 groups. The percentage of patients with serious AEs considered related to the study drug (COBI, 1.7%; RTV, 2.9%), or who discontinued the study drug because of an AE (COBI, 11.0%; RTV, 11.2%) was similar between the 2 treatment arms.

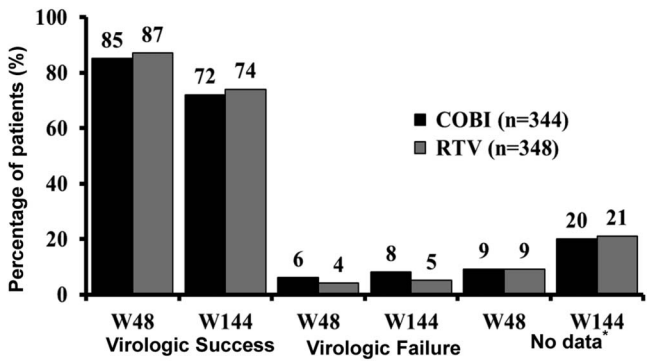

FIGURE 1. Patients achieving virologic success (HIV-1 RNA <50 copies/mL) through weeks 48 and 144. *No data include discontinuation and the last available HIV-1 RNA <50 copies/mL or missing data during window.

TABLE 1. Adverse Events

	COBI (n = 344)		RTV (n = 348)	
	W48	W144	W48	W144
AE (% reported in ≥10% of patients in either group)				
Jaundice	20.9	21.8	15.5	17.2
Scleral icterus	17.7	19.8	18.4	21.8
Nausea	17.7	19.2	16.4	19.0
Diarrhea	15.4	22.4	20.4	27.6
Hyperbilirubinemia	11.3	12.2	9.8	11.2
Headache	11.0	14.5	15.5	20.1
Nasopharyngitis	10.8	15.4	15.2	20.7
URTI	10.2	16.6	8.0	17.8
Fatigue	7.6	10.2	6.9	9.8
Fever	5.5	10.2	7.2	8.9
Back pain	4.7	8.7	6.9	11.2
AE leading to study discontinuation (>1 patient in either group)				
Scleral icterus	2.3	3.5	1.1	1.4
Jaundice	2.6	2.9	2.0	2.0
Hyperbilirubinemia	0.3	0.3	0.6	0.9
Renal abnormalities (proximal tubulopathy)	1.7 (1.5)	2.9 (1.7)	1.4 (0.6)	3.2 (0.6)
Rash	0.3	0.3	0.6	0.6
Allergic dermatitis	0.6	0.6	0	0

Data are % of patients.
URTI, upper respiratory tract infection.

At week 144, a small increase in serum creatinine (median change from baseline +0.13 vs +0.07 mg/dL) and a corresponding decrease in eGFR (median change −15.1 vs −7.5 mL/min) were observed in both groups. These changes occurred by week 4 with little progression between weeks 48 and 144 ($P > 0.05$), consistent with results from studies of EVG/COBI/FTC/TDF and because of inhibition of tubular creatinine secretion. Seven patients (2.0%) in each group developed proximal renal tubulopathy (PRT). In 5 of the 7 patients in the COBI group and 6 of the 7 patients in the RTV group, PRT occurred after week 48. In the COBI-containing regimen, reversibility of renal laboratory abnormalities was seen in 6 of the 7 patients after discontinuation of the study drug (1 patient did not discontinue the study drug). Of those 6 patients, renal laboratories normalized or returned to baseline in 3; among the other 3 subjects with persistent laboratory abnormalities after discontinuation, 2 patients did not have a sufficiently long follow-up period to assess full reversibility and 1 patient started RTV boosted ATV + FTC/TDF.

There were no significant differences between treatment groups from baseline to week 144 in median increase in fasting total cholesterol (+12 vs +16 mg/dL), LDL cholesterol (+9 vs +14 mg/dL), HDL cholesterol (+7 vs +5 mg/dL), or triglycerides (+11 vs +15 mg/dL). Median changes in total cholesterol to HDL cholesterol ratio were also similar (−0.3 vs −0.2).

DISCUSSION

In this randomized double-blinded study, COBI demonstrated persistent and comparable efficacy relative with RTV as a pharmacoenhancer of ATV at week 144. No new safety concerns emerged at week 144. AEs, including bilirubin elevations, jaundice, nausea, and diarrhea, and study drug discontinuations because of AEs were similar in both groups.

Both COBI and RTV inhibit the tubular secretion of creatinine, with no effect on actual GFR.[5–8] Consistent with these findings, a small increase in serum creatinine was seen in both COBI and RTV groups in our study, with COBI having the greater effect. The rates of renal discontinuation in our study were similar to previous studies of TDF-containing boosted PI regimen ranging from 0% to 3%.[9–17] In our study, a small and similar number of patients discontinued the study drug because of PRT [COBI, n = 6 (1.7%) and RTV, n = 7 (2.0%)]. This is consistent with the safety profile of TDF, which has been associated with PRT.[18] In all patients in the COBI group who developed PRT and had follow-up data, tubular abnormalities (proteinuria, glycosuria, or hypophosphatemia) reversed and serum creatinine improved after discontinuation of study medication.

COBI is a mechanism-based inhibitor of cytochrome P450 3A enzymes that is used as pharmacoenhancer of PIs or EVG. The chemical properties of COBI allow for coformulation with other antiretroviral agents such as fixed-dose combination tablets containing EVG, ATV, and darunavir. COBI provides an alternative to RTV as a pharmacoenhancer for antiretroviral therapy containing a PI in adults with HIV-1 infection.

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